ANTI-CD96 ANTIBODIES AND METHODS OF USE THEREOF

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims the benefit under 35 U.S.C. § 119(e) to U.S. Provisional Patent Application Ser. No. 62/783,118, filed on Dec. 20, 2018, the entireties of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The present disclosure relates generally to binding proteins, such as antibodies and antigen-binding fragments, which bind to the CD96 receptor protein and methods of using such binding proteins.

REFERENCE TO SEQUENCE LISTING

[0003] The official copy of the Sequence Listing is submitted concurrently with the specification as an ASCII formatted text file via EFS-Web, with a file name of "09402-003WO1_SeqList_ST25.txt", a creation date of Dec. 16, 2019, and a size of 398,046 bytes. The Sequence Listing filed via EFS-Web is part of the specification and is incorporated in its entirety by reference herein.

BACKGROUND OF THE INVENTION

[0004] CD96 (also known as "TACTILE") is a receptor expressed on the surface of T cells and natural killer (NK) cells. (See e.g., Blake S J, et al., (2016) "Molecular Pathways: Targeting CD96 and TIGIT for Cancer Immunotherapy," Clin Cancer Res 22(21): 5183-8.) CD96 is a member of the Ig superfamily and is further categorized as a member of the nectin/NECL family. CD96 has been found to be expressed in humans on the surface of T cells (ap and yb), NK cells, a subpopulation of B cells, and in mice on T cells, NK cells and NKT cells. CD96 is known to function in concert with CD155, CD226 (also known as "DNAM"), and TIGIT, and is believed to play an important role in inhibiting immune function. The main ligand for CD96 is CD155 to which it binds with a stronger affinity than CD226 binding to CD155, but weaker than TIGIT binding to CD155. Human CD96 exists as two splice variants that exhibit different binding affinities to CD155. (See e.g., Meyer D, et al., (2009) "CD96 interaction with CD155 via its first Ig-like domain is modulated by alternative splicing or mutations in distal Ig-like domains," J Biol Chem 284: 2235-44.) It has been observed that Cd96−/− mice exhibit a hypersensitive NK-cell response to stimulation by LPS, IL12, or IL18, as well as strong resistance to experimental lung metastases and MCA-induced fibrosarcomas. (See e.g., Chan C J, et al., (2014) "The receptors CD96 and CD226 oppose each other in regulation of natural killer cell functions," Nat Immunol 15:431-8.) Anti-CD96 mAbs have been shown to reduce the B16F10 and E0771 lung metastases in mouse models. (See e.g., Blake S J, et al., (2016) "Suppression of metastases using a new lymphocyte checkpoint target for cancer immunotherapy," Cancer Discover 6; 446-59.)

[0005] WO2015/024042A1 (published Feb. 26, 2015) suggests a method of reducing or relieving immune inhibition in a mammal that includes the step of at least partly inhibiting or reducing CD96 activity in one or more cells of the mammal. The suggested method includes a step of administering to the mammal a CD96 inhibitory agent, such as an anti-CD96 antibody, but no anti-CD96 antibodies are described in the disclosure.

[0006] WO2015/024060A1 (published Feb. 26, 2015) also suggests a method of reducing or relieving immune inhibition in a mammal that includes the step of at least partly inhibiting or reducing CD96 activity in one or more cells of the mammal. The disclosure suggests that a commercially available anti-human CD96 antibody "NK92.39" can be effective in increasing IFNγ production in human NK cells, but does not disclose any specific anti-CD96 antibodies that are capable of reducing CD96 activity or tumor growth.

SUMMARY OF THE INVENTION

[0007] The present disclosure provides antibodies that specifically bind human CD96 with high affinity. The antibodies are capable of decreasing, inhibiting, and/or fully-blocking immune regulatory effects mediated by CD96. Additionally, the antibodies are capable of decreasing, inhibiting, and/or fully-blocking immune regulatory function or activity mediated by CD96 binding to CD155. The present disclosure also provides compositions for and methods of treating diseases and conditions responsive to decreasing, inhibiting and/or blocking immune regulatory function or activity mediated by CD96, CD155, CD226, and/or TIGIT.

[0008] In some embodiments, the present disclosure provides an anti-CD96 antibody comprising (i) a first light chain hypervariable region (HVR-L1), a second light chain hypervariable region (HVR-L2), and a third light chain hypervariable region (HVR-L3), and/or (ii) a first heavy chain hypervariable region (HVR-H1), a second heavy chain hypervariable region (HVR-H2), and a third heavy chain hypervariable region (HVR-H3), wherein:

[0009] (a) HVR-L1 comprises an amino acid sequence selected from KASQNVGTAIV (SEQ ID NO: 13), KSSQSLLDSDGKTYLN (SEQ ID NO: 17), RVSQDISFWLS (SEQ ID NO: 21), RASSNVKYMY (SEQ ID NO: 25), KASQSVTFADTGLMH (SEQ ID NO: 29), RSSTGAVTTSNYAN (SEQ ID NO: 33), RASQDIYRNLH (SEQ ID NO: 37), or RASQXIXXNXH (SEQ ID NO: 308), wherein X at position 5 is D, A, E, G, H, K, N, P, Q, S, or T; X at position 7 is Y, or F; X at position 8 is R, K, or Q; X at position 10 is L, I, M, or V;

[0010] (b) HVR-L2 comprises an amino acid sequence selected from SASTRYT (SEQ ID NO: 14), LVSKLDS (SEQ ID NO: 18), KASNLHT (SEQ ID NO: 22), YTSNLAS (SEQ ID NO: 26), RASNLEV (SEQ ID NO: 30), GTNNRAP (SEQ ID NO: 34), HASDSIS (SEQ ID NO: 38), or HAXXXXS (SEQ ID NO: 325), wherein X at position 3 is S, or E; X at position 4 is D, E, K, or Q; X at position 5 is S, H, L, R, or V; X at position 6 is I, or V;

[0011] (c) HVR-L3 comprises an amino acid sequence selected from QQYSSSPLT (SEQ ID NO: 15), LQATHSPQT (SEQ ID NO: 19), LQSQSYPYT (SEQ ID NO: 23), QQFTSSPLT (SEQ ID NO: 27), QQSREYPWT (SEQ ID NO: 31), SLWYGSHWV (SEQ ID NO: 35), LQGYSMPYT (SEQ ID NO: 39), or XQGYXMPXT (SEQ ID NO: 335), wherein X at position 1 is L, G, M, or Q; X at position 5 is S, A, E, Q, or V; X at position 8 is Y, or F;

[0012] (d) HVR-H1 comprises an amino acid sequence selected from TNNWMH (SEQ ID NO: 41), TGYGVT